

## **REMARKS**

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

### **Claim Amendments**

The conformed claims after entry of the amendment appear attached hereto as an Appendix for the convenience of the Examiner.

Claims 1-6, 8, 14, 17-35, 37 and 48-50 are canceled without prejudice. Applicants specifically reserve the right to file a continuing application directed to the canceled subject matter.

Claims 7 and 36 are now directed to an embolic composition that is irradiation sterilized. Support for this amendment is found in ¶ 219 of the specification. Claims 7 and 36 are also amended to specifically recite that the composition includes ethylene vinyl alcohol copolymer, dimethyl sulfoxide which solubilizes the ethylene vinyl alcohol copolymer, and a visualizing effective amount of tantalum. Support for this amendment is found on ¶ 110 (tantalum), ¶ 113 (ethylene vinyl alcohol), and ¶ 120 (dimethyl sulfoxide) of the specification. These claims are further amended to correct some grammatical errors and to read more clearly.

Claims 9-13, 15-16, 38-47 and 51 are amended to recite an “embolic composition” due to amendments made in the base claims from which these claims depend. Various other typographical errors are also corrected by this amendment.

Claims 10-13 and claims 41-44 are amended and now provide the percentage as a change in viscosity over a 6 month or more shelf life. Support for this amendment may be found on ¶ 27 of the specification.

Claim 52 is added and specifies that the rheological modifier is fumed silica. Claims 53 and 54 are added and correlate to claims 7 and 36, respectively, except these claims specify the rheological modifier is fumed silica.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Applicants submit that no new matter is added by this amendment and respectfully request its entry. After amending the claims as set forth above, claims 7, 9-13, 15-16, 36, 38-47, and 51-54 are now pending in this application.

In an effort to expedite prosecution, Applicants have applied the following rejection to the currently presented claims.

**Rejection under 35 U.S.C. § 102(b)**

Claims 7, 9-13, 15-16, 20, 36, and 38-47 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Pat. No. 6,139,819 (hereinafter “Unger”). Applicants respectfully traverse this rejection on the ground that not every limitation recited by the Applicants’ claimed invention is disclosed by Unger.

It is well-settled that to anticipate a claim, a single source must contain all of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986).

Unger describes compositions and methods for a novel diagnostic imaging agent for arrhythmic disorders. The compositions taught by Unger are *aqueous emulsion of liposomes*. The emulsion comprises lipid, protein, polymer or surfactant and a gas. A target ligand in the liposomes delivers the liposome to the intended site (a coagulum, or clot/embolus), and the gas

within the liposome allows for ultrasound detection. Therapeutic methods involve ultrasonic rupture of the liposome *in situ*. Variations are disclosed for incorporating paramagnetic agents in liposomes for MRI detection.

Various sterilization methods (heat, filtration, radiation) are mentioned in Unger at col. 33, Lines 2-10 and at col. 63, lines 56-64 and 31. However, the compositions taught by Unger do not recite every element of the claimed invention. In particular, Unger does not recognize that sterilization by irradiation is preferred over the other methods taught.

In the Action at pages 3-4, the Office states that:

...Applicant's claims clearly overlap in scope with the compositions of Unger, since the two compositions are essentially the same, it is inherent that such a composition will have the same properties...It appears as though applicants are attempting to claim a new function or property of an old composition. Where the claimed and prior art products are identical or substantially identical in structure of composition, or are produced by identical or substantially identical processes, a *prima facie* case [of] either anticipation or obviousness has been established. Thus, the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.

Applicants have amended the claims to recite that the compositions in Claims 7 and 36 require (i) ethylene vinyl alcohol copolymer, dimethyl sulfoxide which solubilizes the ethylene vinyl alcohol copolymer, a visualizing effective amount of tantalum; (ii) hydroxyl-containing rheological modifiers; and (iii) that the composition exhibits a minimal change in its thixotropic behavior after sterilization as compared to the composition prior to sterilization. Further, claims 7 and 36 require that the composition be sterilized by irradiation. Still further, claim 36 requires that 25% of the surface hydroxyl groups are converted to non-hydroxyl groups. Thus, Applicants' claims clearly do not overlap with the compositions of Unger. Nor do the compositions of the currently claimed invention produce identical or substantially identical

compositions thereby establishing anticipation or obviousness, as addressed below in the obviousness rebuttal.

As Unger does not teach every claimed element in claim 7 and 36, Unger does not anticipate the currently claimed invention (i.e., claims 7 and 36 or the claims that depend therefrom).

For the reasons cited above, the Applicants respectfully submit that the rejection under 35 U.S.C. §102(b) is improper and should be withdrawn.

#### **Rejection under 35 U.S.C. § 103(a)**

Claims 7, 9-13, 15-16, 20, 36, and 38-47 and 51 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Unger in view of U.S. Pat. No. 5,580,568 (hereinafter “Greff”) and U.S. Pat. Pub. No. 2003/0039696 (hereinafter “Porter”). Applicants respectfully traverse this rejection on the ground that the Office has not established the *prima facie* case of obviousness.

Assuming *arguendo* that the Office has established a *prima facie* case of obviousness, Applicants rebut this by providing surprising and unexpected results of the compositions currently claimed.

#### **(A) Standard for Determining Obviousness**

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) recently reviewed the analysis for determining if an invention is obvious over the teachings of the prior art and affirmed the factual analysis set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). *KSR*, 127 S. Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18). The factual inquiries necessary in an analysis of obviousness by the Office is delineated in MPEP § 2141 as follows: (A) Determining the scope and contents of the prior art; (B) Ascertaining the

differences between the prior art and the claims in issue; (C) Resolving the level of ordinary skill in the pertinent art; and (D) Evaluating evidence of secondary considerations...

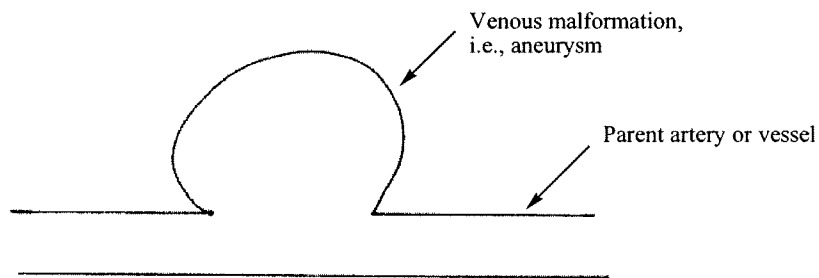
The teaching, suggestion, motivation test for obviousness was also addressed by the Supreme Court in *KSR*, which confirmed that when such a test is applied with flexibility and in a non-mandatory manner, “[t]here is no inconsistency between the idea underlying the [teaching, suggestion, motivation] test and the Graham analysis.”

After application of the facts of Applicants’ invention in the context of the Graham analysis and consistent with the ruling in *KSR*, it will be shown that Applicants’ claimed invention meets the criteria of 35 U.S.C. § 103.

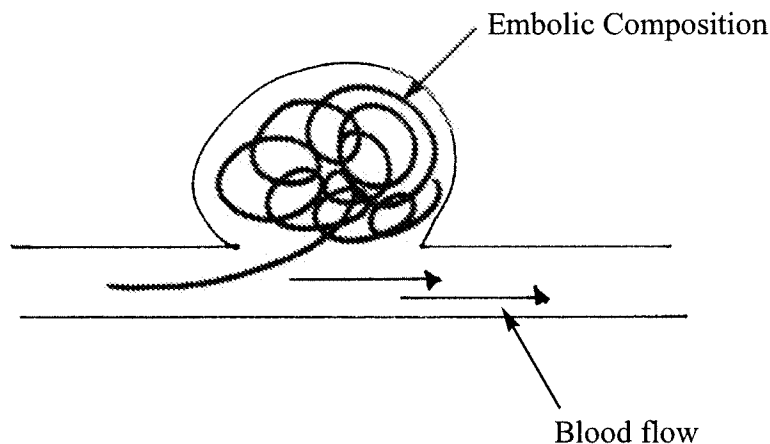
**(B) Applicants’ Rebuttal**

**(1) Applicants’ Claimed Sterilized Compositions**

The currently claimed invention is directed to embolic compositions that have been sterilized by irradiation having a specific rheology profile. The compositions comprise ethylene vinyl alcohol copolymer, dimethyl sulfoxide, tantalum, and a rheological modifier. The compositions of the invention are useful in embolizing blood vessels, i.e. aneurysms. Provided below is a schematic of a vasculature malformation, such as an aneurysm, which could benefit from compositions of the invention.



The biocompatible polymer, ethylene vinyl alcohol copolymer, is soluble in the solvent, dimethyl sulfoxide, but is immiscible in blood. Therefore, when the polymer is delivered to the vascular site, the solvent dissipates leaving a solid polymer mass in the aneurysm. Because the aneurysm is filled with the polymer precipitate, normal blood flow may be resumed in the parent artery. This is best explained by the following diagram:



The composition is delivered to the vascular site via a catheter through complex vasculature. As stated in the specification, the use of high viscosity compositions facilitates the formation of a contiguous or ball-shaped precipitate and provide better control of the aneurysm embolization. See, the specification, ¶ 8. The rheological modifier is added to the composition to ease delivery of the composition by providing non-Newtonian viscosity profiles. The enhanced rheology profiles allow for extremely high viscosity under static conditions (i.e., after delivery of the composition to the vascular site) and much less viscous compositions under shear stress (i.e., during delivery of the composition to the vascular site).

## **(2) Irradiation Sterilization is Surprisingly Better than Heat Sterilization**

As stated in the specification, it has been surprisingly found the compositions sterilized by irradiation have improved rheology profiles because they have minimal thixotropy when compared with the same compositions that have been sterilized by other methods, such as heat. Specifically, compositions of the currently claimed invention retain pseudo-plastic characteristics

after sterilization and the viscosity of the sterilized compositions remain stable over time. See, the specification, ¶ 14. “Both characteristics are essential in order to have predictable compositions for *in vivo* catheter delivery.” See, the specification, ¶ 15. More particularly, the compositions of the invention show little or no deviation in shear stress as the shear rate is varied from 0 to 250 sec<sup>-1</sup>. This deviation, or hysteresis in shear stress as shear rate is increased then decreased, is thixotropy.

As explained in the specification at ¶0008:

Thixotropic compositions are evident by measuring the shear stress (Y axis) against shear rate (X axis) at both increasing and decreasing shear rates and determining the extent of the area generated between the two curves. Compositions exhibiting pseudo-plastic behavior have little or no area between these curves whereas thixotropic compositions have measurable areas between the curves. Specifically, for the purposes of this application, compositions having an area of no more than 25,000 Pa/sec between increasing and decreasing shear rates of from 0 to 250 sec<sup>-1</sup> are deemed to be pseudo-plastic; whereas compositions having an area of greater than 25,000 Pa/sec between increasing and decreasing shear rates of from 0 to 250 sec<sup>-1</sup> are deemed to be thixotropic.

Compositions of the invention have a minimal change in their thixotropic behavior after being sterilized by irradiation. This “minimal change” is represented graphically by an area between curves measuring shear stress at increasing shear rates and decreasing shear rates measured at from 0 to 250 sec<sup>-1</sup>. The area between curves of the compositions currently claimed must be from about 1,000 to about 20,000 Pa/sec. Compositions that are heat sterilized have a much larger area between the curve evidencing a much larger change in thixotropy.

Applicants respectfully direct the Office to Example 7, ¶289 of the instant application. In this Example, embolic compositions falling within the scope of the claim were made, subjected to sterilization by electron beam irradiation or heat, and rheology properties compared. As can be seen in the Table at ¶ 291, the composition that was irradiated had a rheology profile, as

measured by the area between the two curves, that was closer to the control which had not been subjected to any treatment. In fact, the control composition had an area between the two curves that was 2,248 Pa/s and the irradiated composition had an area between the two curves that was 10,684 Pa/s. The heat sterilized composition had an area between the curve that was 36,880 Pa/s, which is 3-times more than the area of the irradiated composition and 16-times more than the area of the control.

As can be seen from this Example, the embolic composition that has been sterilized by irradiation has a superior rheology profile compared with the same embolic composition that has been sterilized with heat. This improved profile provides for an extended shelf life.

### **(3) Superior Properties Could Not have Been Predicted Based on Teachings in the Art**

Applicants submit that this surprising and unexpected properties of irradiated compositions could not have been predicted based on the teachings of Unger. Citation of Greff and Porter do not cure this deficiency.

At best, Unger teaches that a contrast agent may be targeted to tissues in the body for diagnostic imaging and/or for the administration of bioactive agents; however, the compositions taught by Unger are *aqueous emulsion of liposomes*. Unger does not recite an embolic composition ethylene vinyl alcohol copolymer, dimethyl sulfoxide which solubilizes the ethylene vinyl alcohol copolymer, a visualizing effective amount of tantalum that is sterilized by irradiation. While Unger teaches sterilizing liposome compositions, Unger makes no distinction that one method of sterilizing is preferred. Thus, there is no teaching in Unger that sterilizing embolic compositions having ethylene vinyl alcohol copolymer, dimethyl sulfoxide, tantalum, and a rheological modifier by irradiation would produce a composition with minimal thixotropy and extended shelf life.

Porter and Greff also lack this teaching. Specifically, Porter discloses an embolic composition comprising a matrix forming component, a stabilizer, a plasticizer, a contrast agent,



an a rheological modifier. The only matrix forming component described and claimed is an alkyl cyanoacrylate monomer, a chemically reactive prepolymer. There is no mention of sterilizing in Porter. Further, Porter fails to recognize the importance of minimizing the thixotropic behavior of the composition during repeated injection.

Greff is directed to embolic compositions containing cellulose diacetate or triacetate as the precipitating polymer. Note that the polymer is the precipitating polymer and not the rheological modifier. Additionally, the compositions in Greff are sterilized by heat. Greff, like Porter and Unger, did not recognize the importance of minimizing the thixotropic behavior of the composition.

The Office states in the Action, on page 5 that:

It would have been obvious to one skilled in the art that heat could have been used to sterilize the compositions of Unger since the compositions of both references above are related to the same field of endeavor, embolic compositions. The motivation would obviously be to kill or eliminate any transferable agents...so that the agents would not be introduced directly in to the blood stream when the composition is injected to a subject in need.

Applicants respectfully disagree. There is no motivation in Unger to maintain a certain thixotropic behavior in a composition after sterilization to prolong shelf life. Neither Greff nor Porter provide this motivation. As set forth above, the compositions after sterilization should maintain a rheology profile that is similar to the profile before sterilization. Heat sterilized compositions exhibit too drastic of a change in rheology profile which can lend to instability over a prolonged shelf life.

The Office further states on page 6 of the Action that

Porter is used primarily for the disclosure...that rheology modifying agents were already well known in the art at the time of applicant's invention to be useful in embolic compositions. It would have been *prima facie* obvious at the time of the invention to a person of

ordinary skill in the art to modify the embolic composition disclosed in Unger and add the rheological modifying agents disclosed within Greff. It is generally considered to be *prima facie* obvious to combine compounds each of which is taught by the prior art to be useful for the same purpose in order to form a composition that is to be used for an identical purpose. The motivation for combining them flows from their having been used individually in the prior art, and from them being recognized in the prior art as useful for the same purpose. As shown by the recited teachings, [the] instant claims are no more than the combination of conventional components found within embolic compositions. It therefore follows that the instant claimed invention defines *prima facie* obvious subject matter.

As explained above, the instantly claimed invention is not directed to a combination of known or conventional elements because the currently claimed invention requires that the composition have a certain rheology profile (i.e., an area between the curves of from 1,000 Pa/s to 20,000 Pa/s) after it has been sterilized by irradiation. Neither Unger, Greff, nor Porter teach this rheology profile. At best, Unger teaches a heat sterilized composition; however, as demonstrated in the specification (see Example 7), a heat sterilized composition would not have the requisite rheology profile. Further, any showing of a *prima facie* case of obviousness made by the Office is rebutted by a showing of surprising and unexpected results regarding the rheology profile of the compositions.

For the reasons cited above, the Applicants respectfully submit that the rejection under 35 U.S.C. §103(a) is improper and should be withdrawn.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to

Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date April 25, 2008

By Lorna L. Tanner

FOLEY & LARDNER LLP  
Customer Number: 38706  
Telephone: (650) 251-1104  
Facsimile: (650) 856-3710

Lorna L. Tanner  
Attorney for Applicant  
Registration No. 50,782

*Appendix*

*Conformed Claims After Amendment*

1-6. (Canceled)

7. (Currently amended) An embolic composition comprising:

(a) a hydroxyl-containing rheological modifier in an effective amount to impart shear thinning, pseudo-plastic properties to the composition, wherein the modifier is selected from the group consisting of fumed silica, poly(2-hydroxyethylacrylates), copolymers of ethylene and maleic acid, polyvinylalcohol, oxidized poly(alkenes), hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, sodium hydroxyethylcellulose, hydroxyethylcellulose, methylcellulose, poly(2-hydroxyethylmethacrylates), poly(saccharides), poly(siloxanes), carrageenan, guar, xanthan gum, locus bean gum, homo- and co-polymers of mannuronic acid and glucuronic acid and particulate rheological modifiers;

(b) ethylene vinyl alcohol copolymer;

(c) dimethyl sulfoxide which solubilizes the ethylene vinyl alcohol copolymer; and

(d) a visualizing effective amount of tantalum;

wherein the composition is sterilized by irradiation and the composition exhibits a minimal change in its thixotropic behavior after sterilization as compared to the composition prior to sterilization wherein such minimal change is represented graphically by an area between curves measuring shear stress at increasing shear rates and decreasing shear rates measured at from 0 to 250 s<sup>-1</sup> and said area is from about 1,000 to about 20,000 Pa/sec.

8. (Canceled)

9. (Currently amended) The embolic composition according to Claim 7, wherein the area is from about 2,500 to about 15,000 Pa/sec.

10. (Currently amended) The embolic composition according to Claim 7, wherein the sterilized composition is further characterized by exhibiting a change of less than about 25% of its viscosity at 37°C over a shelf-life of 6 months or more at a high shear of 250 sec<sup>-1</sup> as compared to the viscosity under the same conditions immediately after sterilization.

11. (Currently amended) The embolic composition according to Claim 10, wherein the sterilized composition is further characterized by exhibiting a change of less than about 20% of its viscosity at 37°C over a shelf-life of 6 months or more at a high shear of 250 sec<sup>-1</sup> as compared to the viscosity under the same conditions immediately after sterilization.

12. (Currently amended) The embolic composition according to Claim 11, wherein the sterilized composition is further characterized by exhibiting a change of less than about 15% of its viscosity at 37°C over a shelf-life of 6 months or more at a high shear of 250 sec<sup>-1</sup> as compared to the viscosity under the same conditions immediately after sterilization.

13. (Currently amended) The embolic composition according to Claim 12, wherein the sterilized composition is further characterized by exhibiting a change of less than about 10% of its viscosity at 37°C over a shelf-life of 6 months or more at a high shear of 250 sec<sup>-1</sup> as compared to the viscosity under the same conditions immediately after sterilization.

14. (Canceled)

15. (Currently amended) The embolic composition according to Claim 7, wherein the ethylene vinyl alcohol copolymer, dimethyl sulfoxide and tantalum has a viscosity of at least 150 cP at 37°C.

16. (Currently amended) The embolic composition according to Claim 15, wherein the ethylene vinyl alcohol copolymer, dimethyl sulfoxide and tantalum has a viscosity of at least 100 cP at 37°C.

17-35 (Canceled)

36. (Currently amended) An embolic composition comprising:

(a) a hydroxyl-containing rheological modifier in an effective amount to impart pseudo-plastic, shear thinning properties to the composition, wherein the modifier is selected from the group consisting of fumed silica, poly(2-hydroxyethylacrylates), copolymers of ethylene and maleic acid, polyvinylalcohol, oxidized poly(alkenes), hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, sodium hydroxyethylcellulose, hydroxyethylcellulose, methylcellulose, poly(2-hydroxyethylmethacrylates), poly(saccharides), poly(siloxanes), carrageenan, guar, xanthan gum, locus bean gum, homo- and co-polymers of mannuronic acid and glucuronic acid and particulate rheological modifiers;

(b) ethylene vinyl alcohol copolymer,

(c) dimethyl sulfoxide which solubilizes the ethylene vinyl alcohol copolymer; and

(d) a visualizing effective amount of tantalum;

wherein at least about 25% of the surface hydroxyl groups have been converted to non-hydroxyl groups and further wherein said embolic composition is sterilized by irradiation and wherein said embolic composition exhibits a minimal change in its thixotropic behavior after sterilization as compared to the composition prior to sterilization wherein such minimal change is represented graphically by an area between curves measuring shear stress at increasing shear rates and decreasing shear rates measured at from 0 to 250 s<sup>-1</sup> and said area is from about 1,000 to about 20,000 Pa/sec.

37. (Canceled)

38. (Currently amended) The embolic composition according to Claim 36, wherein the area is from about 2,500 to about 15,000 Pa/sec.

39. (Currently amended) The embolic composition according to Claim 36, wherein at least about 50% of the surface hydroxyl groups have been converted to non-hydroxyl groups.

40. (Currently amended) The embolic composition according to Claim 39, wherein at least about 90% of the surface hydroxyl groups have been converted to non-hydroxyl groups.

41. (Currently amended) The embolic composition according to Claim 36, wherein the sterilized composition is further characterized by exhibiting a change of less than about 25% of its viscosity over a shelf-life of 6 months or more at a high shear of  $250 \text{ sec}^{-1}$  as compared to the viscosity under the same conditions immediately after sterilization.

42. (Currently amended) The embolic composition according to Claim 36, wherein the sterilized composition is further characterized by exhibiting a change of less than about 20% of its viscosity over a shelf-life of 6 months or more at a high shear of  $250 \text{ sec}^{-1}$  as compared to the viscosity under the same conditions immediately after sterilization.

43. (Currently amended) The embolic composition according to Claim 42, wherein the sterilized composition is further characterized by exhibiting a change of less than about 15% of its viscosity over a shelf-life of 6 months or more at a high shear of  $250 \text{ sec}^{-1}$  as compared to the viscosity under the same conditions immediately after sterilization.

44. (Currently amended) The embolic composition according to Claim 43, wherein the sterilized composition is further characterized by exhibiting a change of less than about 10% of its viscosity over a 1 year shelf-life.

45. (Canceled)

46. (Currently amended) The embolic composition according to Claim 36, wherein the ethylene vinyl alcohol copolymer, dimethyl sulfoxide and tantalum have a viscosity of at least 150 cP at 37°C.

47. (Currently amended) The embolic composition according to Claim 46, wherein the ethylene vinyl alcohol copolymer, dimethyl sulfoxide and tantalum have a viscosity of at least 100 cP at 37°C.

48-50. (Canceled)

51. (Currently amended) The embolic composition according to Claim 7 or Claim 36, wherein the particulate rheological modifier is selected from the group consisting of hydrophilic fumed silica, silicacious earth, organoclays, and water-swellaable clays.

52. (new) The embolic composition according to Claim 7 or Claim 36, wherein the rheological modifier is hydrophilic fumed silica.

53. (new) An embolic composition comprising:

(a) fumed silica in an effective amount to impart shear thinning, pseudo-plastic properties to the composition,

(b) ethylene vinyl alcohol copolymer;

(c) dimethyl sulfoxide which solubilizes the ethylene vinyl alcohol copolymer; and

(d) a visualizing effective amount of tantalum;

wherein the composition is sterilized by irradiation and the composition exhibits a minimal change in its thixotropic behavior after sterilization as compared to the composition prior to sterilization wherein such minimal change is represented graphically by an area between



curves measuring shear stress at increasing shear rates and decreasing shear rates measured at from 0 to 250 s<sup>-1</sup> and said area is from about 1,000 to about 20,000 Pa/sec.

54. (new) An embolic composition comprising:

(a) fumed silica in an effective amount to impart shear thinning, pseudo-plastic properties to the composition,

(b) ethylene vinyl alcohol copolymer;

(c) dimethyl sulfoxide which solubilizes the ethylene vinyl alcohol copolymer; and

(d) a visualizing effective amount of tantalum;

wherein at least about 25% of the surface hydroxyl groups of the fumed silica have been converted to non-hydroxyl groups and further wherein said embolic composition is sterilized by irradiation and exhibits a minimal change in its thixotropic behavior after sterilization as compared to the composition prior to sterilization wherein such minimal change is represented graphically by an area between curves measuring shear stress at increasing shear rates and decreasing shear rates measured at from 0 to 250 s<sup>-1</sup> and said area is from about 1,000 to about 20,000 Pa/sec.